REMARKS/ARGUMENTS

Claim Status/Support For Claim Amendment

In response to the Office Action of April 7, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim 1 has been amended. Claims 2-38 have been canceled. Claims 39-46 have been added. Claims 1 and 39-46 are pending in the instant application.

No new matter has been added by the amendments to the specification.

The title of the application has been amended to more clearly indicate the invention to which the pending claims are drawn.

The brief description of figure 2 has been amended to include the sequence identification numbers for the sequences shown therein.

Several protocols in the experimental section of the detailed description have been amended to properly identify the trademark SEPHAROSE.

No new matter has been added by the addition of new claims 39-46. New claims 39-46 correspond with cancelled claims 2-38. The above additions to the claims find basis in the original disclosure at page 25, line 16 to page 26, line 22. The method of new claim 39 is described in detail at pages 37-47. Page 47, lines 19-23 refers to use of various types of samples and page 38, line 18 to

page 39, line 8 refers to different mass spectrometric techniques. Page 46, line 19 refers to practicing the claimed methods with a human patient. Pages 47-48 describe kits contemplated for use with the claimed methods. Lines 17-19 on page 47 refer particularly to the immobilizing on solid supports and labeling of components of the contemplated kits. It is clear from these specific recitations and from the description of methods utilized that the methods and types of kits recited in the newly added claims (39-46) were fully contemplated by the inventors at the time of filing and were enabled by virtue of the disclosure as originally filed.

Restriction/Election

Applicants herein affirm the election of Group I (claims 1, 2 and 10-28) without traverse for prosecution on the merits. The election was made during a telephone conference with the Examiner on January 15, 2003.

This application is related in claim format to several pending applications of which serial number 09/846,352 is exemplary. The biopolymer marker of serial number 09/846,352 was found to be novel and subsequently claims reading on methods and kits limited to its use were rejoined with the claims reading on the biopolymer marker under *Ochai*. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner reconsider the restriction requirement in the instant

application to include the new claims (39-46) added herein by amendment. If the peptides of SEQ ID NOS:1-4 are found to be novel, methods and kits limited to their use should also be found novel. Not novel.

Rejections under 35 USC 112 (second paragraph)

Claims 1, 2 and 10-28, as originally presented, stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claims 1, 10, 18 and 28 are vague and confusing in reciting the phrase " at least one analyte thereof" because it is unclear how a material can be an analyte of a biopolymer marker. Claim 1 has been amended and does recite the phrase "at least one analyte thereof". Claims 10, 18 and 28 have been canceled and the phrase "analyte thereof" is not recited in any of the remaining pending claims.

The Examiner alleges that claims 12 and 14 are vague and indefinite in relation to claim 10 in reciting "at least one labeled biochemical material" because it is unclear as to whether the biochemical material in claims 12 and 14 is the same as the biochemical material recited in claim 10, but including a label. Claims 12 and 14 have been canceled and the phrase "at least one labeled biochemical material" is not recited in any of the remaining pending claims.

The Examiner alleges that the term "therefore" in claims 17 and 25 should be --thereof--. Claims 17 and 25 have been canceled and neither "therefore" nor --thereof-- is recited in any of the remaining pending claims.

The Examiner alleges that the term "the sample" in claims 23 and 24 lacks antecedent basis. Claims 23 and 24 have been canceled.

Accordingly, applicants have now clarified the metes and bounds of the claims and respectfully request that all of the above-discussed rejections under 35 U.S.C. 112, second paragraph be withdrawn.

Rejection under 35 USC 112 (first paragraph)

Claims 1, 2 and 10-28, as originally presented, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 has been amended and claims 2 and 10-28 have been canceled. The remaining pending claims are now limited to methods and kits using specific biopolymer markers (SEQ ID NOS:1-4) specifically diagnostic for Alzheimers disease. Applicants are not claiming the ability to predict Alzheimers disease or any other disease state. The instant inventors do not attempt to develop a

reference "normal", but rather strive to specify particular markers which are evidentiary of at least one specific disease state, whereby the presence of said marker serves as a positive indicator of disease (see page 5, lines 12-20 of the instant specification). Applicants claim that the presence of a peptide selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4 is a positive indicator of Alzheimers disease.

The Examiner asserts (on page 4 of the Office Action mailed on April 7, 2003) that the specification does not support that the recited biomarkers (SEQ ID NOS:1-4) positively correlate with Alzheimers disease. Applicants respectfully disagree. Figure 1 shows a photograph of a gel wherein serum samples were run for three subsets of patients; lanes 1-4 show samples of patients having Alzheimers disease, lanes 5-8 show samples of patients not having Alzheimers disease age-matched with the patients(lanes 1-4) who do have Alzheimers disease, lane 9 shows pooled serum from multiple healthy patients and lane 10 shows the measurement standards necessary to interpret the results of the gel. Lanes are read from left to right and are labeled by patient sample as follows; lane 1 is AD-H-S-004; lane 2 is AD-H-S-005; lane 3 is AD-H-S-006; lane 4 is AD-H-S-008; lane 5 is AG-AD-H-S-002; lane 6 is AG-AD-H-S-003; lane 7 is AG-AD-H-S-004; lane 8 is AG-AD-H-S-005; lane 9 is pooled in-house normal and lane 10 is standard molecular weights markers. Contrary to the Examiner's assumption, the bands

on the gel shown in figure 1 do not represent the different peptides (SEQ ID NOS:1-4) but rather represent larger proteins. Fibronectin is shown in figure 1 as band 1. SEQ ID NOS:1-4 represent peptide fragments of fibronectin. It is important to note that the fibronectin band (band 1, figure 1) appears strongest in the samples from age-matched controls, thus supporting the theory of the instant inventors wherein fibronectin is degraded during the disease process of Alzheimers disease. If fibronectin is degraded in the progression of Alzheimers disease, the whole protein will not appear in the serum of the Alzheimers patient and thus will not appear as a strong band on a gel.

The Examiner further asserts that it is not clear how many patient samples were used in this gel. Applicants respectfully disagree, since lanes 1-8 of the gel are labeled with patient numbers in figure 1.

The Examiner asserts that it is not clear how figure 1 was conducted or what source of samples were used. The general procedure for running the gels is shown at page 38 of the instant specification. Additionally, it is believed to be clear that the source of the samples is blood, for example, the gel shown in figure 1 is the HiS 1 (scrub) column, the protocol for which is shown at page 43 wherein it shows clearly in step 1 that the sample is sera.

The Examiner further asserts that there is no evidence which

supports the notion that appearing a different protein certainly attributes to the occurrence of a particular disease. Applicants are not claiming that the peptide markers attribute to the occurrence of a particular disease; Applicants are claiming that the presence of the peptide markers is indicative of Alzheimers disease. Applicants are not required to enable material that is not claimed (see MPEP 2164.08).

The Examiner states that there is a lot of uncertain "missing boxes", *e.g.* different physiological or pathological developments, from protein synthesis down to the phenotype of the specified disease. Applicants claim that the presence of a peptide selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4 is a positive indicator of Alzheimers disease. Applicants are not required to explain the disease process that degrades fibronection in Alzheimers disease; Applicants are only required to show that SEQ ID NOS:1-4 are indicative of Alzheimers disease (see MPEP 2165.03).

The Examiner acknowledges that Figure 1 shows the occurrence of various proteins of the AD disease patients vs. the age-matched controls and that this data supports indicators of disease. Figure 1 shows that the whole fibronectin protein is not found to be present in the sera of Alzheimers patients. Figure 2 shows a trypsin digest of fibronectin band 1 (as extracted from the gel in figure 1)identifying fragments of fibronectin (SEQ ID NOS:1-3)

found in the sera of Alzheimers patients.

In order to further evidence that the claimed biomarker peptides (SEQ ID NOS:1-4) can be used to identify patients having Alzheimers disease, Applicants herein provide the attached Declaration (and Figures) under 37 CFR 1.132. The profiles shown in the figures attached to the declaration indicate that the claimed method can be used to distinguish individuals suffering from Alzheimers disease from those not inflicted with Alzheimers disease. The figures attached to the declaration provide side-by-side profiles (obtained using techniques of mass spectrometry) of normal human sera (top panel of each figure)versus sera from patients having Alzheimers disease (bottom panel of each figure). This profile comparison clearly evidences the absence of the 1356, 1625 and 1629 dalton markers in normal human sera and thus establishes the specificity of the 1356, 1625 and 1629 dalton peptides as markers which when present in the sera are diagnostic for Alzheimers disease.

Accordingly, Applicants assert that one of ordinary skill in the art when reviewing the instant specification and declaration filed herewith would recognize how to use the claimed sequences (SEQ ID NOS:1-4) as markers for Alzheimers disease. Thus, Applicants respectfully request that this rejection now be withdrawn.

Rejection under 35 USC 102(b)

Claim 1, as originally presented, stands rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Bernard *et al.* (Biochemistry 24:2698-2704 1985).

The Examiner alleges that Bernard *et al.* teach isolation and characterization of human cellular fibronectin comprising the sequences SEQ NO:1 and SEQ ID NO:4 of the instant invention (Figure 3 of Bernard *et al.*). Bernard *et al.* also review that fibronectin is etiologically responsible for the pathological development of thrombosis (page 2698, first paragraph of Bernard *et al.*).

Bernard *et al.* teach the isolation of and nucleotide sequences for four overlapping fibronectin cDNA clones prepared from normal human fibroblasts. These cDNA clones encode for the C-terminal one-third of human cellular fibronectin. Bernard *et al.* also compare their data with data from bovine and rat in order to make homology comparisons. Claim 1, as amended herein, recites specific peptides (SEQ ID NOS:1-4) with a specific function (diagnostic for Alzheimers disease). The sequences disclosed by Bernard *et al.* in figure 3 represent entire cDNA clones encoding fibronectin. No where does Bernard *et al.* teach the specific peptides of SEQ ID NOS:1-4 or any other specific fragments of fibronectin. Additionally, Bernard *et al.* do not teach any fibronectin sequence or any portion thereof which is diagnostic for Alzheimer's disease.

Accordingly, Applicants respectfully submit that the claim,

as instantly presented, now distinguish over the compositions taught by Bernard *et al.* and respectfully request that this rejection be withdrawn.

Rejection under 35 USC 103(a)

Claims 10-28, as originally presented, stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bernard *et al.* (Biochemistry 24:2698-2704 1985) in view of Hutchens *et al.* (US 6,225,047 B1).

The Examiner asserts (on page 7 of the Office Action mailed on April 7, 2003) that it would have been obvious to one of ordinary skill in the art at the time that the instant invention was made to combine the teaching of Bernard *et al.* which comprises a biopolymer used as a diagnostic marker of a disease state (Alzheimers disease) with the method of Hutchens *et al.* which uses SELDI-MS for differential detection of biopolymers because the teaching of Hutchens *et al.* specifically taught to resolve different biomarkers for clinical diagnostic purposes.

Bernard *et al.* teach the isolation of and nucleotide sequences for four overlapping fibronectin cDNA clones prepared from normal human fibroblasts. These cDNA clones encode for the C-terminal one-third of human cellular fibronectin. Bernard *et al.* also compare their data with data from bovine and rat in order to make homology comparisons. Claim 1, as amended herein, recites specific

peptides (SEQ ID NOS:1-4) with a specific function (diagnostic for Alzheimers disease). The sequences disclosed by Bernard *et al.* in figure 3 represent entire cDNA clones encoding fibronectin. No where does Bernard *et al.* teach the specific peptides of SEQ ID NOS:1-4 or any other specific fragments of fibronectin. Additionally, Bernard *et al.* do not teach any fibronectin sequence or any portion thereof which is diagnostic for Alzheimers disease. Thus, it is established that Bernard *et al.* do not teach any biopolymer markers diagnostic for Alzheimers disease.

Hutchens *et al.* teach a method for identifying analytes that are differentially present between two samples through the use of the techniques of retentate chromatography and desorption spectrometry. Although the instant invention also teaches a method for identifying analytes that are differentially present between two samples through the use of the techniques of chromatography and spectrometry, the chromatographic methods of the instant invention are distinct from retentate chromatography. Page 45, line 2 of the instant specification refers to the use of micro-chromatographic columns which evidences the use of a form of chromatography known as partition chromatography. Partition chromatography and retentate chromatography are not identical methods. Retentate chromatography is limited by the fact that if unfractionated body fluids (blood, blood products, saliva, urine, cerebrospinal fluid and lymph) along with tissue samples, are applied to the adsorbent surfaces, the

biopolymers present in the greatest abundance will compete for all the available binding sites and thereby prevent or preclude less abundant biopolymers from interacting with them, thereby reducing or eliminating the diversity of biopolymers which are readily ascertainable (see the instant specification at pages 24 and 25). The instant invention is characterized by the use of a combination of preparatory steps (chromatography and 1-D tricine polyacrylamide gel electrophoresis) that maximizes the diversity of biopolymers discernable from a sample thus overcoming the limitation of the retentate chromatography method as taught by Hutchens *et al.* Furthermore, Hutchens *et al.* do not suggest alternative means for the identification of differentially present analytes nor do they suggest preparatory steps to overcome the limitations of retentate chromatography. Thus, even if Bernard *et al.* did disclose biopolymer markers diagnostic for Alzheimers disease and one of ordinary skill in the art identified such markers through use of the methods as taught by Hutchens *et al.*, one of ordinary skill in the art would not have arrived at the instant invention.

There are no teachings or suggestions in either reference (Bernard *et al.* and Hutchens *et al.*) which would motivate one of ordinary skill in the art to use preparatory steps in combination with methods of chromatography and spectrometry to identify any biopolymer markers diagnostic for Alzheimers disease.

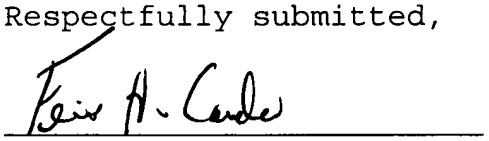
Thus, it is respectfully submitted that the combination of

Bernard *et al.* in view of Hutchens *et al.* fails to reasonably teach or suggest to one of ordinary skill in the art the elements of the invention as specifically set forth in the instantly amended claims.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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